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(54) Method for producing benzylidene derivatives

Verfahren zur Herstellung von Benzyliden-Derivaten

Procédé de préparation de dérivés benzylidène

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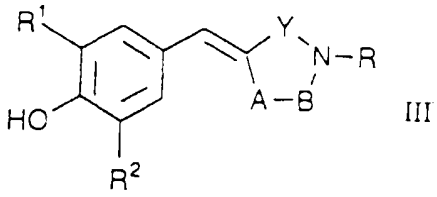
Description

[0001] This invention relates to novel method for producing benzylidene derivatives which have an ability to suppress the production of PGE_2, LTB_4 and IL-1, and can be useful as excellent non-steroidal anti-inflammatory agents

[0002] It is known from FR-A-2 634 764 to react a benzaldehyde with an alpha halocarbonyl compound followed by dehydration of the resulting product as disclosed particularly in the synthesis on page 9 of the specification. Further, EP-A-0 525 197 discloses a process with a witting reagent or an organozinc compound as set forth as production method II on pages 5 and 6 of this specification.

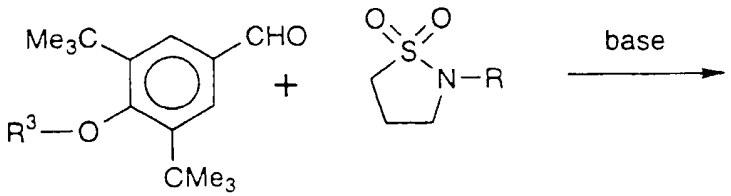
[0003] Benzylidene derivatives represented by the following general formula III



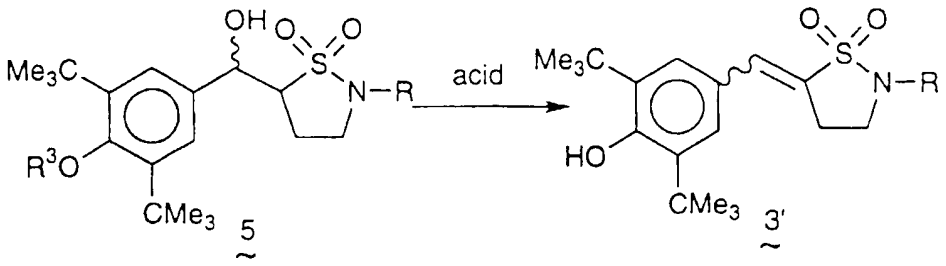
III

wherein R^1 and R^2 each independently is lower alkyl, lower alkoxy or halogen; Y is SO_2, SO or CO; -A- is optionally substituted lower alkylene; -B- is $-CH_2-$ or -O-; or -A- and -B- taken together may form optionally substituted phenylene or optionally substituted lower alkenylene; and R is hydrogen, optionally substituted lower alkyl, cycloalkyl, lower alkoxy, hydroxy, optionally substituted aryl, optionally substituted arylalkyl; optionally substituted arylalkyloxy, heterocyclic ring or N-protecting group are known to include many pharmaceutically useful compounds. For example, it has been suggested that a compound of the formula III wherein -A- is $-CH_2CH_2-$, -B- is -O-, Y is CO, R is $-CH_3$, and R^1 and R^2 are both t-butyl can be useful as an anti-inflammatory agent with low ulcerogenic potential. Sung J. L. et al., Drugs of the Future 17(1): 12-14 (1992); and S. Wong et al., Agents Actions 37: 90-98 (1992). It has also been found that a kind of benzylidene derivatives of the formula III have an ability to suppress the production of PGE_2, LTB_4 and IL-1 in vitro and prevent edema with little damages of gastric mucosa in vivo, and can be excellent non-steroidal anti-inflammatory agents. There are disclosed in EP Appln. No. 93308369.3 (Publication No. 595546) corresponding to USP Appln. No. 08/142,146.

[0004] These benzylidene derivatives of the formula III can be prepared in a conventional manner, for example, according to the following reaction scheme.



4 2



In the reaction scheme above, R is as defined above and R^3 is hydroxy-protecting group in EP Appln. No. 93308369.3 (Publication No. 595546)

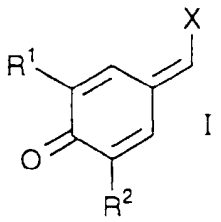
[0005] Thus, hydroxy-protected 3,5-di-tert-butyl-4-hydroxybenzaldehyde 4 is reacted with γ-sultam derivative 2 under a condition for aldol reaction to obtain an aldol addition compound 5. The compound 5, when deprotected and dehydrated in the presence of an acid, gives the objective benzylidene derivative 3' as a mixture of stereoisomers in (E)- and (Z) forms, which is then subjected to resolution, when a given isomer is desired. For example, a compound of the formula 3' wherein R is $-CH_3$ (5-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-methyl-1,2-isothiazolidine-1,1-dioxide), when tested to evaluate inhibitory activity against the production of PGE_2 in rat synovial membrane cells, against the production of LTB_4 in rat celiac cells, or against the production of IL-1 under LPS stimulation in THP-1 cells, showed different activities as follows.

	PGE_2 (Rat SVC)	LTB_4 (Rat PEC)	L-1 (THP-1)	IC_{50} (μM)
(E)	<0.001	2.8	21	
(Z)	<0.001	1.8	29	

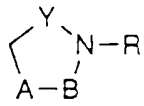
[0006] The separation of isomers of compounds shown by the formula III, however, is difficult and requires troublesome procedures, which prevented the industrial production of the benzylidene derivatives. Therefore, a novel method for producing compounds III, especially an isomer thereof, which is stereoselective and applicable to industrial processes, has been required to promote the development of medicinal drugs, especially steroidal anti-inflammatory agents.

[0007] The present inventors have made intensive researches in order to establish a method for producing selectively a desired isomer of a compound of the formula III and found that a desired stereoisomer of high purity can be prepared in high yield by reacting a quinone methide compound and a nitrogen-containing heterocyclic compound in the presence of a base.

[0008] Thus, the present invention provides a method for producing benzylidene derivatives of the formula III, which comprises reacting a compound of the formula I:



wherein R^1 and R^2 each independently is lower alkyl, lower alkoxy or halogen; and X is lower alkoxy or halogen with a compound of the formula II:



II

wherein-Y-is SO_2, SO or CO; -A- is optionally substituted lower alkylene; -B- is $-CH_2-$ or -O-; or -A- and -B- taken together may form optionally substituted phenylene or optionally substituted lower alkenylene; and R is hydrogen, optionally substituted lower alkyl, cycloalkyl, lower alkoxy, hydroxy, optionally substituted aryl, optionally substituted arylalkyl; optionally substituted arylalkyloxy, heterocyclic ring or N-protecting group in the presence of a base.

[0009] According to the method of the present invention, a desired pharmaceutically active benzylidene derivative of the formula III can be obtained in stereoselective manner by treating a quinone methide compound of the formula I (i.e., 4-methylene-2,5-cyclohexadienone derivative) substituted with a leaving group X with an anion prepared by treating a heterocyclic compound of the formula II with a base such as an organolithium compound.

[0010] For purposes of the present invention, as disclosed and claimed herein, the following terms are defined below.

[0011] The term "lower alkyl" means straight or branched chain C_1 - C_8 alkyl, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, neopentyl, s-pentyl, t-pentyl, n-hexyl, neohexyl, i-hexyl, s-hexyl, t-hexyl, heptyl and octyl. Preferable lower alkyl groups are straight or branched chain C_1 - C_4 alkyl and the most preferred are methyl or ethyl.

[0012] The term "lower alkoxy" means straight or branched chain alkoxy of 1 to 6 carbon atoms, for example, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, n-pentyloxy, i-pentyloxy, neopentyloxy, s-pentyloxy, t-pentyloxy, n-hexyloxy, neohexyloxy, i-hexyloxy, s-hexyloxy and t-hexyloxy. Preferable lower alkoxy groups are C_1 - C_3 alkoxy and the most preferred one is methoxy.

[0013] The term "halogen" means fluorine, chlorine, bromine and iodine and the preferred one is chlorine.

[0014] The term "lower alkylene" means a group formed by taking a hydrogen atom from each carbon at both ends of a linear alkane of C_1 - C_5, preferably, C_1 - C_4. Examples of lower alkylene available and preferred are methylene, ethylene and propylene.

[0015] The term "lower alkenylene" means a group formed by taking a hydrogen atom from each carbon at both ends of a linear alkene of C_2 - C_5, preferably, C_2 - C_4. Examples of lower alkenylene available and preferred are vinylene, propenylene, butenylene.

[0016] The substituents in the definition of "optionally substituted phenylene" are halogen, lower alkyl, lower alkoxy.

[0017] Substituents in the definition of "optionally substituted alkylene" are lower alkyl, hydroxyalkyl, alkoxyalkyl, lower alkoxy, hydroxy, phenyl.

[0018] Substituents in the definition of "optionally substituted alkenylene" are lower alkyl, hydroxyalkyl, alkoxyalkyl, lower alkoxy, phenyl.

[0019] The term "heterocyclic ring" means a cyclic group containing 1 - 4 hetero atoms selected from sulfur, nitrogen and oxygen, for example, pyridyl, furfuryl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl and tetrazolyl.

[0020] The term "cycloalkyl" means cycloalkyl of 3 - 7 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A C_3 - C_5 cycloalkyl, particularly cyclopropyl, is preferred.

[0021] The term "aryl" means phenyl or naphthyl. As defined by the term "optionally substituted aryl", aryl may have one or more substituents selected from halogen, lower alkoxy, lower alkyl, nitro and trifluoromethyl. Examples of optionally substituted aryl include phenyl, 4-chlorophenyl, 4-methoxyphenyl, 4-methylphenyl, 4-nitrophenyl, 3,4-dichlorophenyl, 3,4-dimethoxyphenyl, 3,4-dinitrophenyl, 1-naphthyl and 2-naphthyl.

[0022] The term "arylalkyl" means a group formed by substituting a lower alkyl group as defined above with an aryl group(s), which may be substituted with one or more substituent(s) described in the definition for "optionally substituted aryl". Examples of optionally substituted arylalkyl include benzyl, 4-chlorobenzyl, 4-methoxybenzyl, 4-methylbenzyloxy, 3,4-dichlorobenzyl, 3,4-dimethoxybenzyl, 4-nitrobenzyl, 2-phenylethyl, 2-(4-chlorophenyl)ethyl, 2-(4-methoxyphenyl) ethyl, 1-naphtylmethyl and 2-naphtylmethyl with a preference for benzyl.

[0023] The term "arylalkyloxy" means a group formed by substituting a lower alkoxy group as defined above with an aryl group(s), which may be substituted with one or more substituent(s) described in the definition for "optionally substituted aryl". Examples of optionally substituted arylalkyloxy include benzyloxy, 4-chlorobenzyloxy, 4-methoxybenzyloxy, 4-methylbenzyloxy, 3,4-dichlorobenzyloxy, 3,4-dimethoxybenzyloxy, 4-nitrobenzyloxy, 2-phenylethyloxy, 2-(4-chlorophenyl)ethyloxy, 2-(4-methoxyphenyl)ethyloxy, 1-naphtylmethyloxy and 2-naphtylmethyloxy with a preference for benzyloxy.

[0024] Substituents in the definition of "substituted lower alkyl" are halogen, hydroxy, lower alkoxy, amino, lower alkylamino, di-lower-alkylamino.

[0025] N-protecting groups usable in the present method can be selected from those conventionally used in the art, for example, tert-butoxycarbonyl, benzyloxycarbonyl, benzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 4-nitrobenzyl, trimethylsilyl, dimethyl-tert-butylsilyl, diphenyl-tert-butylsilyl.

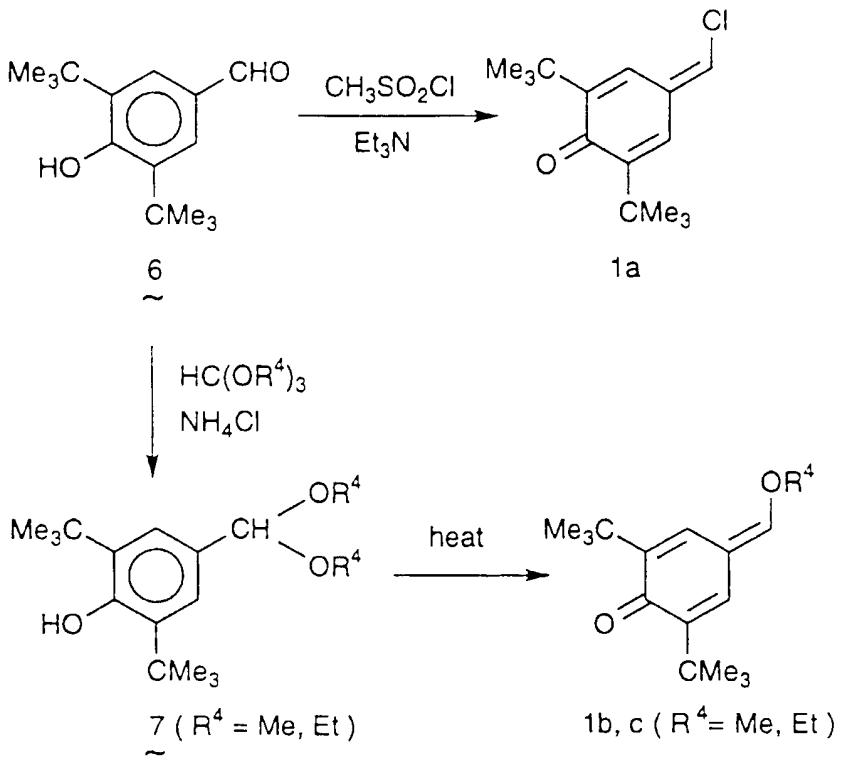
[0026] Bases usable in the present invention include organolithium compounds such as n-butyllithium, sec-butyllithium, tert-butyllithium, phenyllithium, lithium diisopropylamide (LDA), lithium bis(trimethylsilyl)amide (LiHMDS) and the like. LDA and LiHMDS are preferred.

[0027] The present methods can be effected by using any starting compounds I and II though, there are certain preferable compounds, for example, compounds I wherein X is lower alkoxy, especially methoxy, and compounds II wherein Y is SO_2. The most preferred compound to be produced is (E)-5-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-ethyl-1,2-isothiazolidine-1,1-dioxide.

[0028] The method of the present invention will be explained below in detail employing certain compounds to facilitate understanding. These compounds are used simply for illustrative purpose, and one of ordinary skill in the art can easily determine that any compounds of the formula III can be prepared according to the present invention by selecting appropriate starting materials.

Step 1

[0029]



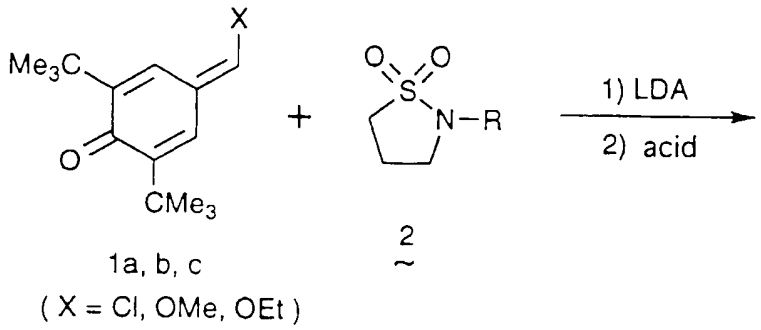
[0030] The starting material, quinone methide 1 (i.e., 4-substituted methylene-2,6-di-tert-butyl-2,5-cyclohexadiene-1-one) (compound I) can be prepared by any one of known methods in the art. Thus, compounds of the formula I wherein X is halogen and those wherein X is lower alkoxy can be prepared according to teachings in USP No. 5,093,363 corresponding to EP Publication No. 414206 and J. Org. Chem. 35, 3714-3717 (1970), respectively, as shown in the reaction scheme above.

[0031] Compound 1a (4-chloromethylene-2,6-di-tert-butyl-2,5-cyclohexadiene-1-one) can be obtained by treating 3,5-Di-tert-butyl-4-hydroxybenzaldehyde 6 with methane sulfonyl chloride in the presence of triethylamine.

[0032] Compounds 1b and 1c wherein R^4 is methyl and ethyl, respectively are readily obtained by converting compound 6 into acetal compound 7 in a conventional manner and heating the resultant compound 7.

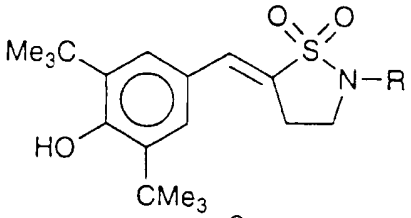
Step 2: Reaction of Compounds I and II

[0033]



1a, b, c
(X = Cl, OMe, OEt)

2



3

[0034] Prior to the reaction, compound (2) is treated with a base, especially with an organolithium compound, to allow to generate an anion. Examples of organolithium compounds usable in the present method include those commonly used in the field of organic chemistry such as n-butyllithium, sec-butyllithium, tert-butyllithium, phenyllithium, lithium diisopropylamide (LDA), lithium bis(trimethylsilyl)amide (LiHMDS) and the like. Reaction is carried out in a solvent selected from ether solvents such as ether, tetrahydrofuran (THF), dimethoxyethane, dioxane and the like; and hydrocarbon solvents such as n-hexane, benzene, toluene and the like, or a mixture thereof, in the presence of hexamethylphosphoramide (HMPA), tetramethylethylenediamine and the like, preferably in a single solvent of THF.

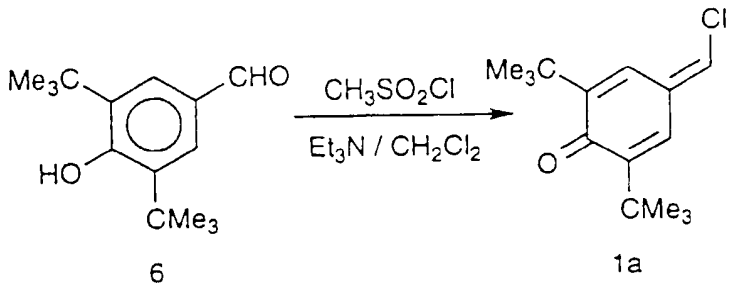
[0035] About 0.1 to 2 equivalents, preferably 0.5 to 1 equivalent of a quinone methide prepared in step 1 (e.g., compound 1a-c) is reacted with an anion of compound 2 prepared above at about -100 to 50°C, preferably at -70 to 0°C until the reaction is complete. The resultant product is treated with an appropriate acid to give the desired compound 3. Example of acids usable include inorganic acids such as hydrochloride and organic acids such as p-toluenesulfonic acid.

[0036] The following Examples are provided to further illustrate the present invention and are not to be construed as limiting thereof.

Preparation 1

Preparation of 4-Chloromethylene-2,6-di-tert-butyl-2,5-cyclohexadiene-1-one (1a)

[0037]

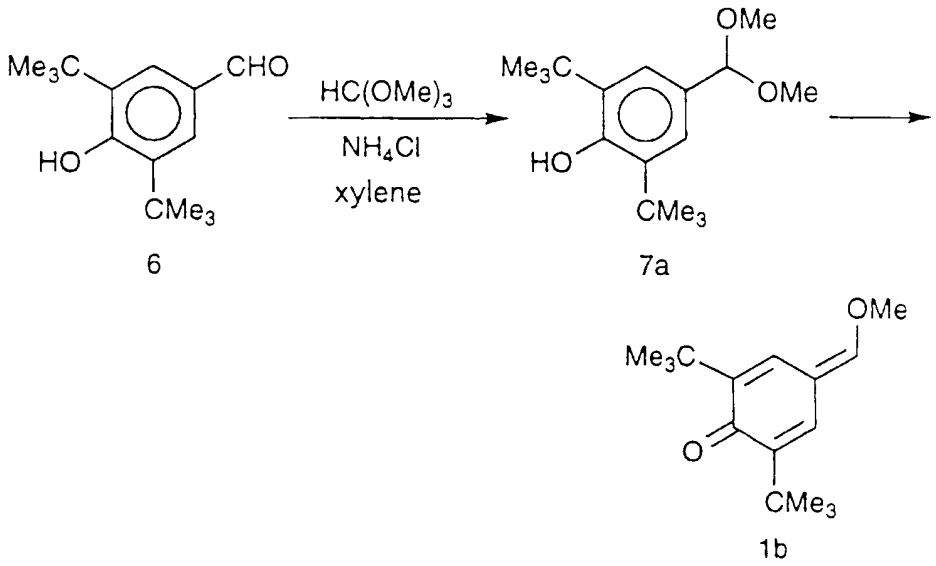


[0038] To a solution of 3,5-di-tert-butyl-4-hydroxybenzaldehyde (6) (7.02 g, 30 mmole) in methylene chloride (70 ml) was added dropwise triethylamine (8.36 ml, 60 mmole). After the addition of methanesulfonyl chloride (4.7 ml, 60 mmole), the mixture was heated to reflux for 5 hr. The resultant reaction mixture was concentrated under reduced pressure to yield the crude product (1a) (8.156 g), which was used in the next step without further purification. NMR($CDCl_3$)δppm: 1.28(9H, s), 1.32(9H, s), 6.81(1H, d, J=2.4Hz), 7.42(1H, d, J=2.4Hz).

Preparation 2

Preparation of 2,6-di-tert-Butyl-4-methoxymethylene-2,5-cyclohexadiene-1-one (1b)

[0039]



[0040] To anhydrous xylene (60 ml) were added compound (6) (23.4 g, 0.1 mole), ethyl orthoformate (60 ml) and absolute methanol (60 ml) successively. After addition of ammonium chloride (2 g), the mixture was heated to reflux

for 1 hr. The resultant reaction mixture was concentrated at ordinary pressure to distill off about 150 ml of solvent. The residue was cooled to room temperature by adding anhydrous xylene (200 ml) and filtered through cotton plug to remove ammonium chloride. The filtrate was heated to reflux for 24 hr in Dean-Stark apparatus equipped with 4A molecular sieves and concentrated under reduced pressure to yield brown crystalline residue. The residue, when recrystallized from a mixture of petroleum ether and ligroin, gave the objective compound (1b) (20.32 g, 82 %). M.p. 137-139°C.
NMR (D_6-acetone) δppm: 1.61(9H, s), 1.64(9H, s), 4.43(3H, s), 3.68(1H, d, J=2.2Hz), 7.76-7.82(2H, m).

Preparation 3

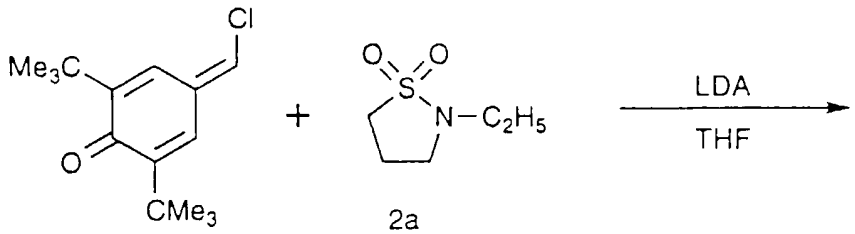
Preparation of 2,6-di-tert-Butyl-4-ethoxymethylene-2,5-cyclohexadiene-1-one (1c)

[0041] Compound (6) (23.4 g, 0.1 mole), ethyl orthoformate (60 ml), absolute methanol (60 ml) and ammonium chloride (2 g) were reacted in anhydrous xylene (60 ml) and the resultant reaction mixture was treated in a manner similar to that described in Preparation 2 to yield the objective compound (1c) (22.01 g, 84 %). M.p. 114-117°C.
NMR (D_6-acetone) δppm: 1.61(9H, s), 1.64(9H, s), 1.75(3H, t, J=7.0Hz), 4.69(2H, q, J=7.0Hz), 3.68(1H, d, J=2.2Hz), 7.76-7.82(2H, m).

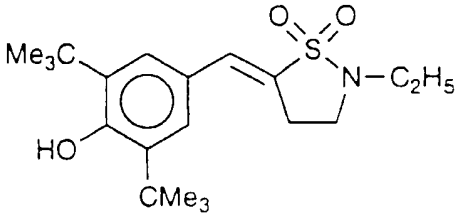
Example 1

Preparation of (E)-5-(3,5-di-tert-Butyl-4-hydroxybenzylidene)-2-ethyl-1,2-isothiazolidine-1,1-dioxide (3a) by Method (A)

[0042]



1a 2a



3a

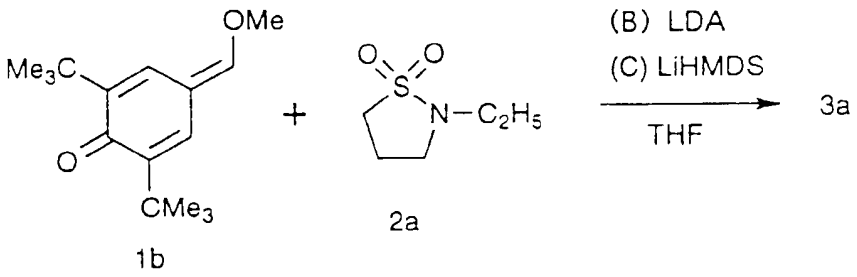
[0043] Lithium diisopropylamide (hereinafter, referred to as LDA) solution was prepared by adding dropwise diisopropylamine (10.58 ml, 73 mmole) to a solution of n-butyllithium in n-hexane (1.68 M, 39 ml, 66 mmole) with stirring and ice-cooling over 20 min followed by stirring for another 15 min. The LDA solution was cooled to -78°C and combined with THF (60 ml) and hexamethylphosphoramide (hereinafter, referred to as HMPA) (12 ml). To the resultant solution was added dropwise a solution of N-ethyl-1,2-isothiazolidine-1,1-dioxide (2a) (4.47 g, 30 mmole) in THF (30 ml) at -70 to -65°C, and the mixture stirred at -70°C for 30 min. To the reaction mixture was added dropwise a solution of crude 4-chloromethylene-2,6-di-tert-butyl-2,5-cyclohexadiene-1-one (1a) (30 mmole) prepared in Preparation 1 above in THF (30 ml) at -70 to -65°C. After stirring at -70°C for 30 min and then at room temperature for 1 hr, the reaction mixture was poured into ice-cooled water containing 2N HCl (40 ml) and extracted with ethyl acetate (350 ml) (x2). The ethyl

acetate solution was washed with water (50 ml) (x3) and a saturated brine (50 ml), dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue (12.73 g) was dissolved in toluene (150 ml). To the solution was added p-toluensulfonic acid (p-TsOH) hydrate (1.87 g, 9.8 mmole) and the mixture heated to reflux for 30 min. The reaction mixture was poured into dilute aqueous solution of sodium hydrogencarbonate (100 ml) and extracted with ethyl acetate (300 ml). The organic layer was washed with water (150 ml) followed by a saturated brine (150 ml), dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue, when purified by the use of column chromatography on silica gel eluting with toluene/ethyl acetate (2:1) and recrystallized from dichloromethane/diisopropyl ether, gave 1.86 g (17 %) of the objective compound (3a). M.p. 135-137°C. NMR ($CDCl_3$) δppm: 1.29(3H, t, J=7.2Hz), 1.45(18H, s), 3.07-3.19(4H, m), 3.28(2H, q, J=7.2Hz), 5.50(1H, s), 7.24-7.26 (3H, m).

Elementary analysis ($C_{20}H_{31}NO_3S$)				
Calcd.	C, 65.71;	H, 8.55;	N, 3.83;	S, 8.77
Found	C, 65.65;	H, 8.43;	N, 3.85;	S, 8.78.

Example 2

[0044] **Preparation of Compound (3a) by Methods (B) and (C)**



(1) Method (B)

LDA solution was prepared by adding dropwise diisopropylamine (29.72 ml, 0.21 mole) to a solution of n-butyllithium in n-hexane (1.60 M, 125 ml, 0.2 mole) with stirring and ice-cooling over 20 min followed by stirring for another 15 min. The LDA solution was cooled to -78°C and combined with THF (320 ml). To the resultant solution was added dropwise a solution of N-ethyl-1,2-isothiazolidine-1,1-dioxide (2a) (29.84 g, 0.2 mole) in THF (60 ml) at -70 to -65°C. After stirring at -70°C for 30 min, to the reaction mixture was added dropwise a solution of 2,6-di-tert-butyl-4-methoxymethylene-2,5-cyclohexadiene-1-one (1b) (24.8 g, 0.1 mole) prepared in Preparation 2 above in THF (60 ml) at -70 to -65°C. The reaction mixture was warmed to -30°C and stirred for 2.5 hr, poured into ice-cooled water containing 2N HCl (226 ml) and extracted with ethyl acetate (500 ml) (x2). The organic layer was washed with water (200 ml) and a saturated brine (200 ml), dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue (48.77 g), when recrystallized from dichloromethane/diisopropyl ether, gave 30.2 g (83 %) of the objective compound (3a).

(2) Method (C)

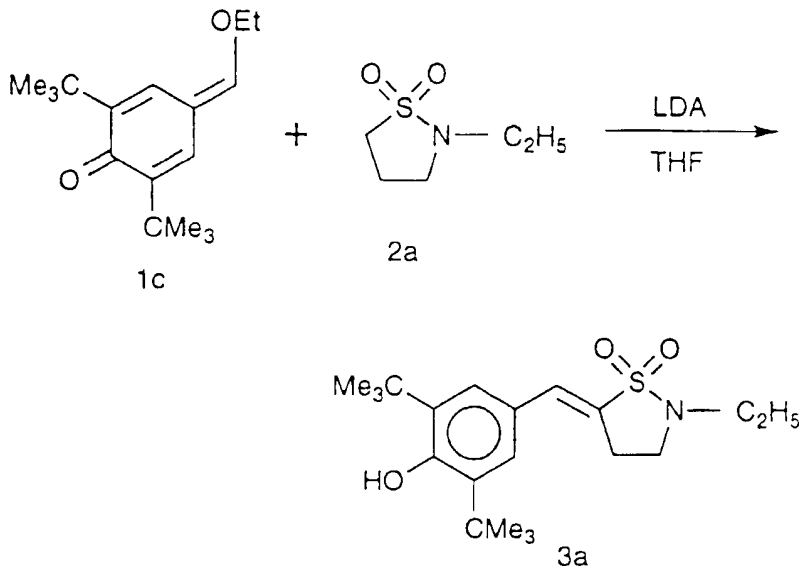
Procedures herein employed were substantially the same as those described in Method (B) above except that lithium bis(trimethylsilyl)amide (LiHMDS) was used instead of LDA.

To a solution of compound (2a) (7.625 g, 51.1 mmole) in THF (50 ml) was added dropwise a solution of LiHMDS (1.0 M in THF) (56.2 ml, 56.2 mmole) with stirring and ice-cooling and the resultant mixture stirred at room temperature for 30 min. To the reaction mixture was added dropwise a solution of compound (1b) (6.35 g, 25.5 mmole) prepared in Preparation 2 above in THF (60 ml) with stirring and cooling at -55 to -48°C. The reaction mixture was gradually warmed to room temperature over about 1 hr. After the reaction is complete, the reaction product was treated in a similar manner as that described in (1) above to yield the objective compound (3a) (5.0 g, 54 %).

Example 3

Preparation of Compound (3a) by Method (D)

[0045]

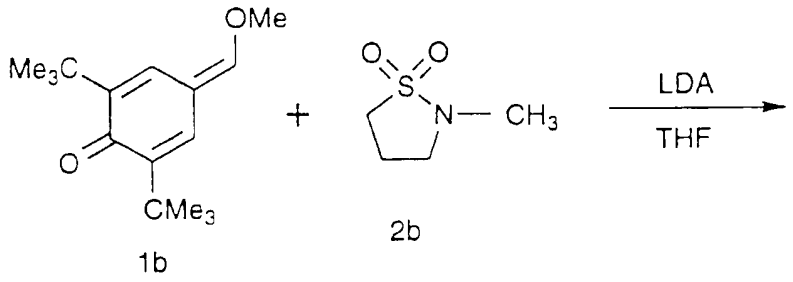


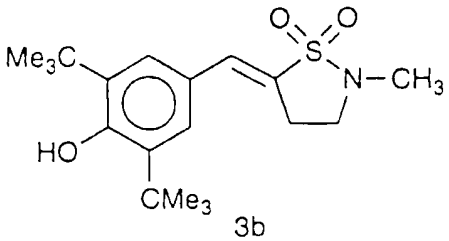
[0046] LDA solution was prepared by adding dropwise diisopropylamine (7.43 ml, 52.5 mmole) to a solution of n-butyllithium in n-hexane (1.60 M, 31 ml, 50 mmole) with stirring and ice-cooling over 20 min followed by stirring for another 15 min. The LDA solution was cooled to -78°C and combined with THF (80 ml). To the resultant solution was added dropwise a solution of compound (2a) (7.46 g, 50 mmole) in THF (15 ml) at -70 to -65°C and stirred at -70°C for 30 min. To the reaction mixture was added dropwise a solution of 2,6-di-tert-butyl-4-ethoxymethylene-2,5-cyclohexadiene-1-one (1c) (6.56 g, 25 mmole) prepared in Preparation 3 in THF (15 ml) at -70 to -65°C. The reaction mixture was warmed to -30°C, stirred for 4.0 hr, poured into ice-cooled water containing 1N HCl (130 ml), and extracted with ethyl acetate (300 ml) (x2). The organic layer was washed with water (100 ml) and a saturated brine (200 ml), dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue (13.8 g), when recrystallized from dichloromethane/diisopropyl ether, gave 6.01 g (66 %) of the objective compound (3a).

Example 4

Preparation of (E)-5-(3,5-di-tert-Butyl-4-hydroxybenzylidene)-2-methyl-1,2-isothiazolidine-1,1-dioxide (3b)

[0047]





3b

[0048] LDA solution was prepared by adding dropwise diisopropylamine (9.34 ml, 72 mmole) to a solution of n-butyllithium in n-hexane (1.60 M, 39 ml, 66 mmole) with stirring and ice-cooling over 20 min followed by stirring for another 15 min. The LDA solution was cooled to -78°C and combined with THF (160 ml). To the resultant solution was added dropwise a solution of N-methyl-1,2-isothiazolidine-1,1-dioxide (2b) (8.96 g, 60 mmole) in THF (40 ml) at -70 to -65°C and the mixture stirred at -70°C for 30 min. To the reaction mixture was added dropwise a solution of compound (1b) (7.45 g, 30 mmole) prepared in Preparation 2 above in THF (40 ml) at -70 to -65°C. After stirring at -70°C for 1 hr, the reaction mixture was poured into ice-cooled water containing 1N HCl (170 ml) and extracted with ethyl acetate (300 ml) (x2). The organic layer was washed with water (200 ml) and a saturated brine (200 ml), dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue (17.8 g) was dissolved in toluene (350 ml). To the solution was added p-toluenesulfonic acid (p-TsOH) hydrate (3.70 g, 19.5 mmole) and the mixture heated to reflux for 30 min at 125°C. The reaction mixture was poured into saturated aqueous solution of sodium hydrogencarbonate (150 ml) and extracted with ethyl acetate (150 ml). The organic layer was washed with saturated aqueous solution of sodium hydrogencarbonate (150 ml), water (100 ml) and a saturated brine (100 ml), dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue, when recrystallized from dichloromethane/diisopropyl ether to give 7.31 g (69 %) of the objective compound (3b). M.p. 168-170°C.

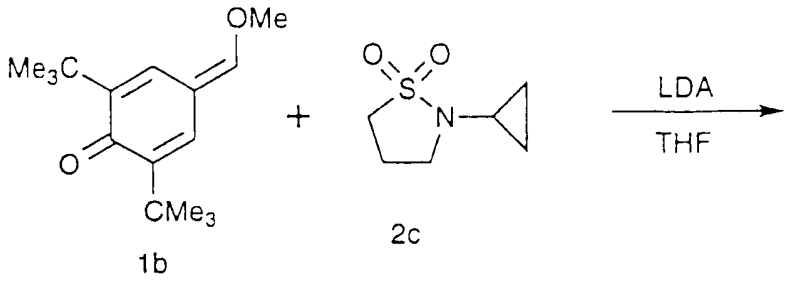
NMR ($CDCl_3$) δppm: 1.45(18H, s), 2.76(3H, s), 3.07-3.18(2H, m), 3.20-3.32(2H, m), 5.51(1H, s), 7.23-7.29(3H, m).

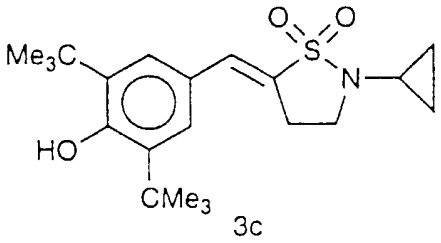
Elementary analysis ($C_{19}H_{29}NO_3S$)				
Calcd.	C, 65.71;	H, 8.55;	N, 3.83;	S, 8.77
Found	C, 65.65;	H, 8.43;	N, 3.85;	S, 8.78

Example 5

Preparation of 2-Cyclopropyl-5-(3,5-di-tert-Butyl-4-hydroxybenzylidene)-1,2-isothiazolidine-1,1-dioxide (3c)

[0049]





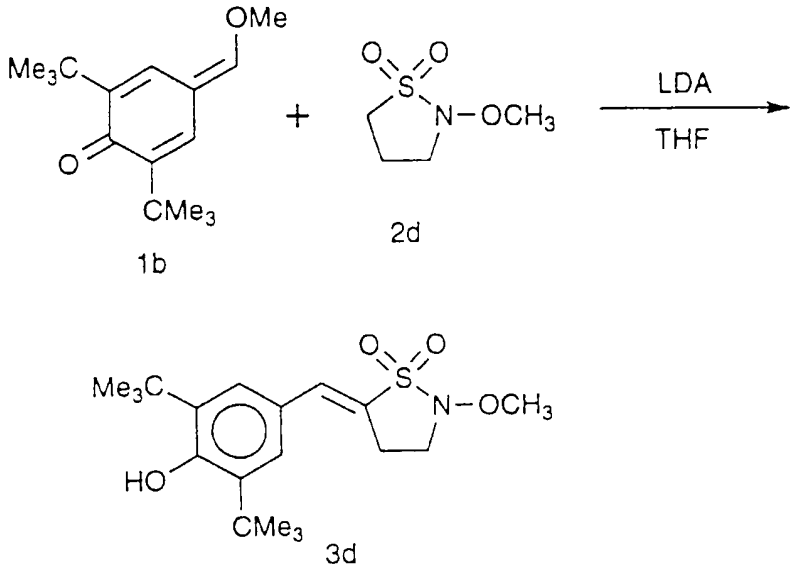
[0050] In accordance with the method described in Example 2 (1) above, the objective compound (3c) was obtained by preparing LDA solution from a solution of n-butyllithium in n-hexane (1.60 M, 12.5 ml, 20 mmole) and diisopropylamine (2.97 ml, 21 mmole), adding THF (20 ml) to the LDA solution, reacting the resultant mixture with a solution of N-cyclopropyl-1,2-isothiazolidine-1,1-dioxide (2c) (3.22 g, 20 mmole) in THF (10 ml) and then with a solution of compound (1b) (2.48 g, 10 mmole) in THF (10 ml), and treating the resultant reaction mixture in the same manner as described above. Yield, 2.57 g (68 %); m.p. 202-204°C.
NMR ($CDCl_3$) δppm: 0.68-0.90(4H, m), 1.44(18H, s), 2.28-2.40(1H, m), 3.08(2H, dt, J=2.6, 6.7Hz), 3.36(2H, t, J=6.7Hz), 5.51(1H, s), 7.20-7.25(3H, m).

Elementary analysis ($C_{21}H_{31}NO_3S$)				
Calcd.	C, 66.81;	H, 8.28;	N, 3.71;	S, 8.49
Found	C, 66.76;	H, 8.03;	N, 3.72;	S, 8.41.

Example 6

Preparation of 5-(3,5-di-tert-Butyl-4-hydroxybenzylidene)-2-methoxy-1,2-isothiazolidine-1,1-dioxide (3d)

[0051]



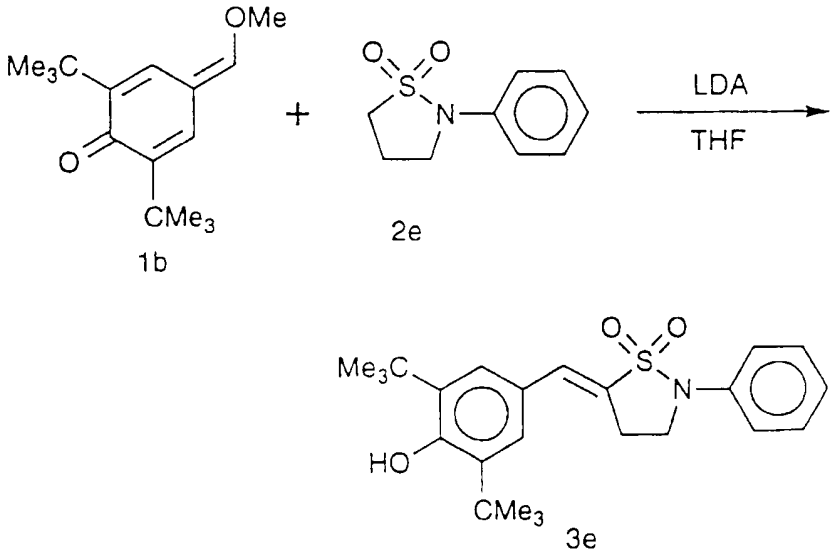
[0052] In accordance with the method described in Example 2 (1) above, the objective compound (3d) was obtained by preparing LDA solution from a solution of n-butyllithium in n-hexane (1.60 M, 12.5 ml, 20 mmole) and diisopropylamine (2.97 ml, 21 mmole), adding THF (20 ml) to the LDA solution, reacting the resultant mixture with a solution of N-methoxy-1,2-isothiazolidine-1,1-dioxide (2d) (2.48 g, 20 mmole) in THF (10 ml) and then with a solution of compound (1b) (2.48 g, 10 mmole) in THF (10 ml), and treating the resultant reaction mixture in the same manner as described above. Yield, 2.46 g (67 %); m.p. 166-168°C.
NMR ($CDCl_3$) δppm: 1.45(18H, s), 3.11(2H, dt, J=2.8, 7.0Hz), 3.66(2H, t, J=7Hz), 3.81(3H, s), 5.55(1H, s), 7.25-7.35 (3H, m).

Elementary analysis ($C_{19}H_{29}NO_4S$)				
Calcd.:	C, 62.10;	H, 7.95;	N, 3.81;	S, 8.72
Found :	C, 61.90;	H, 7.88;	N, 3.91;	S, 8.67.

Example 7

Preparation of (E)-5-(3,5-di-tert-Butyl-4-hydroxybenzylidene)-2-phenyl-1,2-isothiazolidine-1,1-dioxide (3e)

[0053]



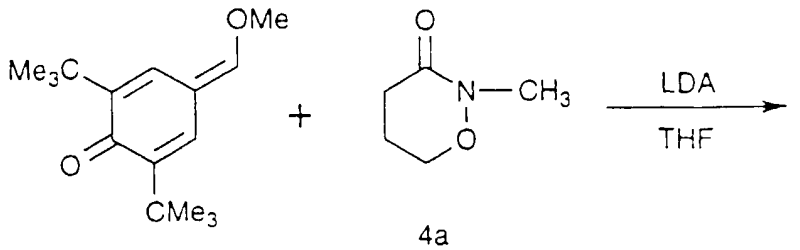
[0054] In accordance with the method described in Example 2 (1) above, the objective compound (3e) was obtained by preparing LDA solution from a solution of n-butyllithium in n-hexane (1.60 M, 12.5 ml, 20 mmole) and diisopropylamine (2.97 ml, 21 mmole), adding THF (20 ml) to the LDA solution, reacting the resultant mixture with a solution of N-phenyl-1,2-isothiazolidine-1,1-dioxide (2e) (3.95 g, 20 mmole) in THF (10 ml) and then with a solution of compound (1b) (2.48 g, 10 mmole) in THF (10 ml), and treating the resultant reaction mixture in the same manner as described above. Yield, 2.27 g (55 %); m.p. 195 - 196°C
NMR ($CDCl_3$) δppm: 1.47(18H, s), 3.31(2H, d, t, J=2.6, 6.6Hz), 3.80(2H, t, J=6.6Hz), 5.54(1H, s), 7.17-7.26(3H, m).

Elementary analysis ($C_{24}H_{31}NO_3S$)				
Calcd.	C, 69.70;	H, 7.56;	N, 3.39;	S, 7.75
Found	C, 69.68;	H, 7.47;	N, 3.32;	S, 7.71.

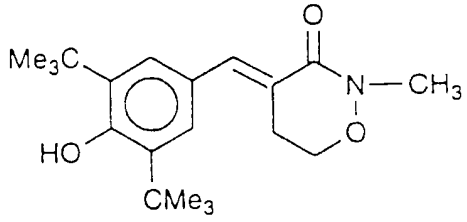
Example 8

Preparation of (E)-4-(3,5-di-tert-Butyl-4-hydroxybenzylidene)-2-methyl-3,4,5,6-tetrahydro-1,2-oxazin-3-one (3f)

[0055]



1b 4a



3f

[0056] In accordance with the method described in Example 2 (1) above, a solution of LDA in THF (710 ml) was prepared from a solution of n-butyllithium in n-hexane (1.63 M, 174 ml, 283.6 mmole) and diisopropylamine (37.8 ml, 283.5 mmole), to which were added dropwise a solution of compound (1b) (31.1 g, 270 mmole) in THF (200 ml) and compound (4a) (26.8 g, 108 mmole) in THF (300 ml) successively with stirring and cooling at -50 to -55°C, and the resultant reaction mixture was gradually warmed up to room temperature over about 1.5 hr. The reaction mixture was treated with a saturated aqueous solution of ammonium chloride (1.2 l) and extracted with ethyl acetate (1.2 l). The ethyl acetate extract was washed with water (1 l), dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was chromatographed on silica gel. The objective compound (3f), which is a known compound in Drugs of the Future 17 (1): 12-14 (1992), was obtained from fractions eluted with n-hexane/ethyl acetate (5:1). Yield, 15.19 g (42 %); m.p., 174 - 176°C.

IR (KBR) cm^{-1}: 3223, 1642, 1574, 1437, 1194.

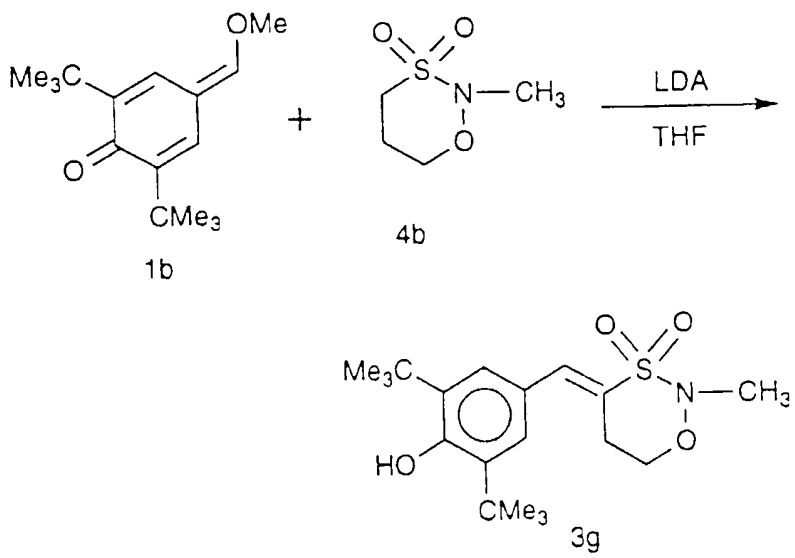
NMR ($CDCl_3$) δppm: 1.45(18H, s, 2 × ^{t}Bu), 3.04(2H, dt, J=2.2, 6.0Hz, CH2), 3.35(3H, s, CH3), 4.20(2H, t, J=6.0Hz, CH2), 5.45(1H, s, OH), 7.32(2H, s, 2ü~ ArH), 7.76(1H, t, J=2.2Hz, CH).

Elementary analysis ($C_{20}H_{29}NO_3$)			
Calcd.	C, 72.47;	H, 8.82;	N, 4.23
Found	C, 72.43;	H, 8.86;	N, 4.29.

Example 9

Preparation of (E)-6-(3,5-di-tert-Butyl-4-hydroxybenzylidene)-2-methyl-4,5-dihydro-6H-1,3,2-thiaoxazin-1,1-dioxide (3g)

[0057]



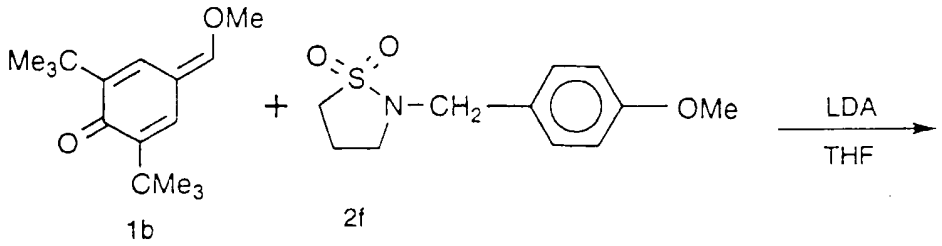
[0058] In accordance with the method described in Example 2 (1) above, to a solution of LDA prepared from a solution of n-butyllithium in n-hexane (1.60 M, 2.5 ml, 20 mmole) and diisopropylamine (2.97 ml, 21 mmole) was added THF (20 ml) and the resultant solution was reacted with a solution of compound (4b) (3.03 g, 20 mmole) in THF (10 ml) and compound (1b) (2.48 g, 10 mmole) in THF (10 ml) successively. The resultant reaction mixture was treated in a similar manner as above to yield the objective compound (3g). Yield, 2.31 g (63 %); m.p., 215 - 216.5°C.
NMR ($CDCl_3$) δppm: 1.44(18H, s, 2 × Bu^t), 3.00(3H, s, CH3), 3.26-3.32(2H, m, CH2), 4.12-4.17(2H, m, CH2), 5.49 (1H, s, OH), 7.15(2H, s, Ar-H), 7.55(1H, broad, CH).

Elementary analysis ($C_{19}H_{29}NO_4S$)				
Calcd.	C, 62.10;	H, 7.95;	N, 3.81;	S, 8.72
Found	C, 62.03;	H, 7.91;	N, 3.92;	S, 8.51.

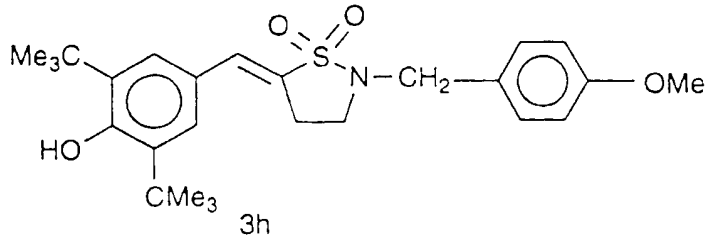
Example 10

Preparation of (E)-5-(3,4-di-tert-Butyl-4-hydroxybenzylidene)-2-(4-methoxybenzyl)-1,2-isothiazolidine-1,1-dioxide (3h)

[0059]



1b 2f



3h

[0060] In accordance with the method described in Example 2 (1) above, to a solution of LDA prepared from a solution of n-butyllithium in n-hexane (1.60 M, 81 ml, 0.130 mole) and diisopropylamine (18.5 ml, 0.132 mole) was added THF (80 ml) and the resultant solution was reacted with a solution of compound (2f) (28.98 g, 0.120 mole) in THF (120 ml) and compound (1b) (15 g, 60 mmole) in THF (120 ml) successively. The resultant reaction mixture was treated in a similar manner as above to yield the objective compound (3h). Yield, 25.55 g (93 %); m.p., 189 - 192°C.
NMR ($CDCl_3$) δppm: 1.44(18H, s, 2 × Bu^t), 3.03-3.18(4H, m, 2 × CH_2), 3.81(3H, s, OMe), 4.16(2H, s, CH2), 5.50(1H, s, OH), 6.88(2H, d, J=8.8Hz, 2 × Ar-H), 7.24-7.27(5H, m, 4 × Ar-H+CH).

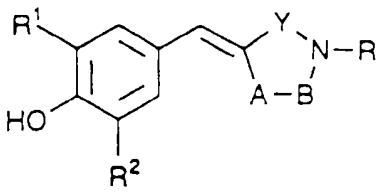
Elementary analysis ($C_{26}H_{35}NO_4S$)				
Calcd.	C, 68.24;	H, 7.71;	N, 3.06;	S, 7.01
Found	C, 68.08;	H, 7.70;	N, 3.08;	S, 6.96.

[0061] As is described above, the present invention provides a method for effective and stereoselective preparation of benzylidene derivatives of the formula III including pharmaceutically useful compounds such as non-steroidal anti-inflammatory agents in high yield, and thereby rendering industrial production thereof available and contributing to the improvement of researches and development of medicinal drugs.

[0062] The invention also includes a method of producing a pharmaceutical composition having anti-inflammatory activity wherein a compound in accordance with formula III of claim 1 is prepared using a method as claimed in anyone of claims 1 to 7 and thereafter said compound is formulated with a diluent, excipient or carrier to provide said composition.

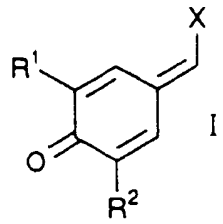
Claims

1. A method for producing compounds of the formula III:



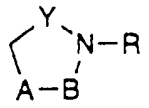
III

wherein R^1 and R^2 each independently is straight or branched chain C_1-C_8 alkyl, straight or branched chain C_1-C_6 alkoxy or halogen; Y is SO_2, SO or CO; -A- is optionally substituted linear alkylene having up to 5 carbon atoms; -B- is $-CH_2-$ or -O-; or -A- and -B- taken together may form optionally substituted phenylene or optionally substituted linear alkenylene of 2 to 5 carbon atoms; and R is hydrogen, optionally substituted straight or branched chain C_1-C_8 alkyl, cycloalkyl having 3-7 carbon atoms, straight or branched chain C_1-C_6 alkoxy, hydroxy, optionally substituted phenyl or naphthyl, optionally substituted arylalkyl which is straight or branched chain C_1-C_8 alkyl substituted with a phenyl or naphthyl group; optionally substituted arylalkyloxy which is straight or branched chain C_1-C_6 alkoxy substituted with phenyl or naphthyl, heterocyclic ring which is a cyclic group containing 1-4 carbon atoms selected from sulfur, nitrogen and oxygen or N-protecting group, which comprises reacting a compound of the formula I:



I

wherein R^1 and R^2 are as defined above and X is straight or branched chain C_1-C_6 alkoxy or halogen with a compound of the formula II:



II

wherein Y, -A-, -B- and R are as defined above in the presence of a base, wherein:

(1) the optional substituent(s) for optionally substituted linear alkylene are straight or branched chain C_1-C_8 alkyl or hydroxy alkyl, alkoxy alkyl with the alkoxy being a straight or branched chain C_1-C_6 alkoxy and the alkyl being a straight or branched chain C_1-C_8 alkyl, straight or branched C_1-C_6 alkoxy, hydroxy or phenyl;
(2) the optional substituent(s) for optionally substituted phenylene are halogen, straight or branched chain C_1-C_8 alkyl, or straight or branched chain C_1-C_6 alkoxy;
(3) the optional substituent(s) for optionally substituted linear alkenylene are straight or branched chain C_1-C_8 alkyl or hydroxy alkyl, alkoxyalkyl with the alkoxy being a straight or branched chain C_1-C_6 alkoxy and the alkyl being a straight or branched chain C_1-C_8 alkyl, straight or branched chain C_1-C_6 alkoxy or phenyl;
(4) the optional substituent(s) for the optionally substituted straight or branched chain C_1-C_8 alkyl are halogen, hydroxy, straight or branched chain C_1-C_6 alkoxy, amino, lower alkylamino or di-lower-alkylamino with lower alkyl of these substituted aminos being straight or branched chain C_1-C_8 alkyl;
(5) the optional substituent(s) for optionally substituted phenyl or naphthyl are halogen, straight or branched chain C_1-C_6 alkoxy, straight or branched chain C_1-C_8 alkyl, nitro or trifluormethyl;
(6) the optional substituent(s) for optionally substituted aryl of arylalkyl are those specified in (5); and
(7) the optional substituent(s) for optionally substituted aryl of arylalkoxy are those specified in (5).

2. The method as claimed in claim 1, wherein X is straight or branched chain C_1-C_6 alkoxy.

3. The method as claimed in claim 2, wherein X is methoxy.

4. The method as claimed in claim 1, wherein Y is SO_2.

5. The method as claimed in claim 1, wherein the base is an organolithium compound.

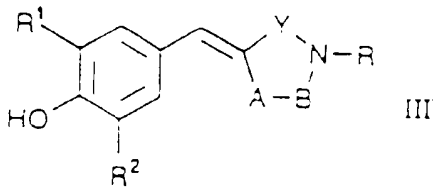
6. The method as claimed in claim 5, wherein the base is lithium diisopropylamide or lithium bis(trimethylsilyl)amide.

7. The method as claimed in claim 1, wherein the reactants are such as to produce (E)-5-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-ethyl-1,2-isothiazolidine-1,1-dioxide, as the compound of formula III.

8. A method of producing a pharmaceutical composition having anti-inflammatory activity wherein a compound in accordance with formula III of claim 1 is prepared using a method as claimed in any one of claims 1 to 7 and thereafter said compound is formulated with a diluent, excipient or carrier to provide said composition.

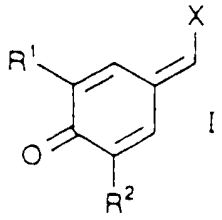
Patentansprüche

1. Verfahren zum Herstellen von Verbindungen der Formel III:



III

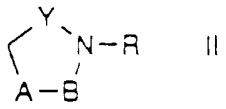
in der R^1 und R^2 jeweils unabhängig voneinander einen unverzweigten oder verzweigten C_1-C_6-Alkylrest, einen unverzweigten oder verzweigten C_1-C_6-Alkoxyrest oder ein Halogenatom bedeuten, Y SO_2, SO oder CO darstellt, -A- eine gegebenenfalls substituierte lineare Alkylengruppe mit bis zu 5 Kohlenstoffatomen bedeutet, -B- $-CH_2-$ oder -O- darstellt oder -A- und -B- zusammengenommen eine gegebenenfalls substituierte Phenylengruppe oder gegebenenfalls substituierte lineare Alkenylengruppe mit 2 bis 5 Kohlenstoffatomen bilden können und R ein Wasserstoffatom, einen gegebenenfalls substituierten unverzweigten oder verzweigten C_1-C_6-Alkylrest, einen Cycloalkylrest mit 3 - 7 Kohlenstoffatomen, einen unverzweigten oder verzweigten C_1-C_6-Alkoxyrest, eine Hydroxygruppe, eine gegebenenfalls substituierte Phenyl- oder Naphthylgruppe, einen gegebenenfalls substituierten Arylalkylrest, der ein mit einer Phenyl- oder Naphthylgruppe substituierter unverzweigter oder verzweigter C_1-C_6-Alkylrest ist, einen gegebenenfalls substituierten Arylalkyloxyrest, der ein mit einer Phenyl- oder Naphthylgruppe substituierter unverzweigter oder verzweigter C_1-C_6-Alkoxyrest ist, einen heterocyclischen Ring, der ein cyclischer Rest mit 1-4 Heteroatomen, ausgewählt aus Schwefel, Stickstoff und Sauerstoff, ist, oder eine N-Schutzgruppe darstellt, wobei das Verfahren das Umsetzen einer Verbindung der Formel I:



I

in der R^1 und R^2 wie vorstehend definiert sind, und X einen unverzweigten oder verzweigten C_1-C_6-Alkoxyrest

oder ein Halogenatom bedeutet, mit einer Verbindung der Formel II:



II

in der Y, -A-, -B- und R wie vorstehend definiert sind, in Gegenwart einer Base umfaßt, wobei:

(1) der/die wahlfreie(n) Substituent(en) eines gegebenenfalls substituierten linearen Alkylenrests unverzweigte oder verzweigte C_1-C_8 -Alkylreste oder Hydroxyalkylreste, Alkoxyalkylreste, wobei der Alkoxyrest ein unverzweigter oder verzweigter C_1-C_6-Alkoxyrest ist und der Alkylrest ein unverzweigter oder verzweigter C_1-C_8-Alkylrest ist, unverzweigte oder verzweigte C_1-C_6-Alkoxyreste, eine Hydroxy- oder Phenylgruppe ist/sind;

(2) der/die wahlfreie(n) Substituent(en) einer gegebenenfalls substituierten Phenylengruppe Halogenatome, unverzweigte oder verzweigte C_1-C_8-Alkylreste oder unverzweigte oder verzweigte C_1-C_6-Alkoxyreste ist/sind;

(3) der/die wahlfreie(n) Substituent(en) einer gegebenenfalls substituierten linearen Alkenylengruppe unverzweigte oder verzweigte C_1-C_8-Alkylreste oder Hydroxyalkylreste, Alkoxyalkylreste, wobei der Alkoxyrest ein unverzweigter oder verzweigter C_1-C_6-Alkoxyrest ist und der Alkylrest ein unverzweigter oder verzweigter C_1-C_8-Alkylrest ist, unverzweigte oder verzweigte C_1-C_6-Alkoxyreste oder eine Phenylgruppe ist/sind;

(4) der/die wahlfreie(n) Substituent(en) eines gegebenenfalls substituierten unverzweigten oder verzweigten C_1-C_8-Alkylrests Halogenatome, eine Hydroxygruppe, unverzweigte oder verzweigte C_1-C_6-Alkoxyreste, eine Aminogruppe, ein Niederalkylaminorest oder ein Diniederalkylaminorest ist/sind, wobei Niederalkylreste dieser substituierten Aminogruppen unverzweigte oder verzweigte C_1-C_8-Alkylreste sind;

(5) der/die wahlfreie(n) Substituent(en) einer gegebenenfalls substituierten Phenyl- oder Naphthylgruppe Halogenatome, unverzweigte oder verzweigte C_1-C_6 -Alkoxyreste, unverzweigte oder verzweigte C_1-C_8-Alkylreste, eine Nitro- oder Trifluormethylgruppe ist/sind;

(6) der/die wahlfreie(n) Substituent(en) eines gegebenenfalls substituierten Arylrests eines Arylalkylrestes der/die in (5) angegebene(n) ist/sind; und

(7) der/die wahlfreie(n) Substituent(en) eines gegebenenfalls substituierten Arylrests eines Arylalkoxyrestes der/die in (5) angegebene(n) ist/sind.

2. Verfahren nach Anspruch 1, wobei X einen unverzweigten oder verzweigten C_1-C_6-Alkoxyrest bedeutet.

3. Verfahren nach Anspruch 2, wobei X eine Methoxygruppe darstellt.

4. Verfahren nach Anspruch 1, wobei Y SO_2 bedeutet.

5. Verfahren nach Anspruch 1, wobei die Base eine Organolithiumverbindung ist.

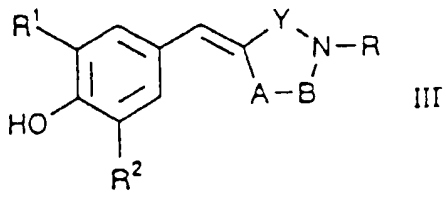
6. Verfahren nach Anspruch 5, wobei die Base Lithiumdiisopropylamid oder Lithiumbis(trimethylsilyl)amid ist.

7. Verfahren nach Anspruch 1, wobei die Umsetzungspartner solche sind, daß (E)-5-(3,5-Di-tert.-butyl-4-hydroxybenzyliden)-2-ethyl-1,2-isothiazolidin-1,1-dioxid als Verbindung der Formel III hergestellt wird.

8. Verfahren zum Herstellen eines Arzneimittels mit entzündungshemmender Wirkung, wobei eine Verbindung gemäß Formel III des Anspruchs 1 unter Verwendung eines Verfahrens nach einem der Ansprüche 1 bis 7 hergestellt wird, und die Verbindung danach mit einem Verdünnungsmittel, Excipient oder Träger formuliert wird, um das Arzneimittel bereitzustellen.

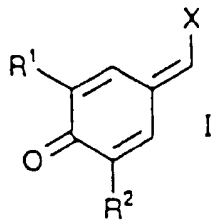
Revendications

1. Procédé pour préparer des composés de formule III:



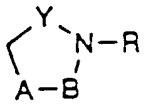
III

dans laquelle R^1 et R^2 sont chacun indépendamment un alkyle en C_1-C_8 à chaîne linéaire ou ramifiée, un alcoxy en C_1-C_6 à chaîne linéaire ou ramifiée ou un halogène; Y est SO_2, SO ou CO; -A- est un alkylène linéaire ayant jusqu'à 5 atomes de carbone éventuellement substitué; -B- est $-CH_2-$ ou -O-; ou -A- et -B- pris ensemble peuvent former un phénylène éventuellement substitué ou un alcénylène linéaire de 2 à 5 atomes de carbone éventuellement substitué; et R est un hydrogène, un alkyle en C_1-C_8 à chaîne linéaire ou ramifiée éventuellement substitué, un cycloalkyle ayant 3 à 7 atomes de carbone, un alcoxy en C_1-C_6 à chaîne linéaire ou ramifiée, un hydroxy, un phényle ou naphtyle éventuellement substitué, un arylalkyle, éventuellement substitué, qui est un alkyle en C_1-C_8 à chaîne linéaire ou ramifiée substitué avec un groupe phényle ou naphtyle; un arylalkyloxy, éventuellement substitué, qui est un alcoxy en C_1-C_6 à chaîne linéaire ou ramifiée substitué avec un phényle ou un naphtyle, un hétérocycle qui est un groupe cyclique contenant 1 à 4 hétéroatomes choisis parmi le soufre, l'azote et l'oxygène ou un groupe protecteur de N, qui comprend une étape consistant à faire réagir un composé de formule I:



I

dans laquelle R^1 et R^2 sont tels que définis ci-dessus et X est un alcoxy en C_1-C_6 à chaîne linéaire ou ramifiée ou un halogène, avec un composé de formule II:



II

dans laquelle Y, -A-, -B- et R sont tels que définis ci-dessus, en présence d'une base, dans lequel :

(1) le(s) substituant(s) éventuel(s) pour l'alkylène linéaire éventuellement substitué sont un alkyle ou hydroxyalkyle en C_1-C_8 à chaîne linéaire ou ramifiée, un alcoxyalkyle avec l'alcoxy qui est un alcoxy en C_1-C_6 à chaîne linéaire ou ramifiée et l'alkyle qui est un alkyle en C_1-C_8 à chaîne linéaire ou ramifiée, un alcoxy en C_1-C_6 linéaire ou ramifié, un hydroxy ou un phényle;
(2) le(s) substituant(s) éventuel(s) pour le phénylène éventuellement substitué sont un halogène, un alkyle en C_1-C_8 à chaîne linéaire ou ramifiée, ou un alcoxy en C_1-C_6 à chaîne linéaire ou ramifiée;
(3) le(s) substituant(s) pour l'alcénylène linéaire éventuellement substitué sont un alkyle ou hydroxyalkyle en C_1-C_8 à chaîne linéaire ou ramifiée, un alcoxyalkyle avec l'alcoxy qui est un alcoxy en C_1-C_6 à chaîne linéaire ou ramifiée et l'alkyle qui est un alkyle en C_1-C_8 à chaîne linéaire ou ramifiée, un alcoxy en C_1-C_6 à chaîne

linéaire ou ramifiée ou un phényle;
(4) le(s) substituant (s) éventuel(s) pour l'alkyle en C_1-C_8 à chaîne linéaire ou ramifiée éventuellement substitué sont un halogène, un hydroxy, un alcoxy en C_1-C_6 à chaîne linéaire ou ramifiée, un amino, un alkyl(inférieur) amino ou di-alkyl(inférieur)amino avec l'alkyle inférieur de ces amino substitués qui est un alkyle en C_1-C_8 à chaîne linéaire ou ramifiée;
(5) le(s) substituant(s) éventuels pour le phényle ou naphtyle éventuellement substitué sont un halogène, un alcoxy en C_1-C_6 à chaîne linéaire ou ramifiée, un alkyle en C_1-C_8 à chaîne linéaire ou ramifiée, un nitro ou un trifluorométhyle;
(6) le(s) substituant(s) éventuels pour l'aryle éventuellement substitué de l'arylalkyle sont ceux spécifiés dans (5); et
(7) le(s) substituant(s) éventuels pour l'aryle éventuellement substitué de l'arylalcoxy sont ceux spécifiés dans (5).

2. Procédé selon la revendication 1, dans lequel X est un alcoxy en C_1-C_6 à chaîne linéaire ou ramifiée.

3. Procédé selon la revendication 2, dans lequel X est un méthoxy.

4. Procédé selon la revendication 1, dans lequel Y est SO_2.

5. Procédé selon la revendication 1, dans lequel la base est un composé organolithium.

6. Procédé selon la revendication 5, dans lequel la base est le diisopropylamide de lithium ou le bis(triméthylsilylamide) de lithium.

7. Procédé selon la revendication 1, dans lequel les réactifs sont tels qu'ils produisent le (E)-5-(3,5-di-tert-butyl-4-hydroxybenzylidène)-2-éthyl-1,2-isothiazolidine-1,1-dioxyde, en tant que composé de formule III.

8. Procédé de préparation d'une composition pharmaceutique ayant une activité anti-inflammatoire dans lequel un composé selon la formule III de la revendication 1 est préparé en utilisant un procédé selon l'une quelconque des revendications 1 à 7 et après cela ledit composé est formulé avec un diluent, un excipient ou un support pour fournir ladite composition.